3 Rotaxanes with diphenylmethane blocking groups[†]

3.1 Introduction

In order to synthesize well-defined oligorotaxanes with a mechanically linked backbone, a method involving sequential deprotection and coupling steps of a biprotected rotaxane monomer was presented in chapter 2. After selecting the most suitable type of rotaxane, the esterification was chosen as the appropriate coupling reaction. Studies on model compounds with a TBDPS-protected phenol and either a THP-protected or an allyl-protected carboxylic acid have shown that both combinations can be used in the rotaxane monomer.

In the first section of this chapter, we will describe the synthesis of this rotaxane monomer, based on cyclophane–polyether thread that bears a TBDPS-protected phenol in the dumbbell and a THP protected carboxylic acid in the cyclophane. The characterization by UV–Vis and NMR spectroscopy and MALDI-TOF mass spectrometry will be discussed, as well as the study of the reactivity of the carboxylic acid group in the cyclophane towards esterification. We will see that the low yield in the 'clipping' procedure, the low stability of the THP protective group and the low reactivity of the carboxylic acid can all be related to a combination of electronic effects of the electron-withdrawing pyridinium moieties and steric effects. In order to resolve the last two problems, we have redesigned the rotaxane monomer.

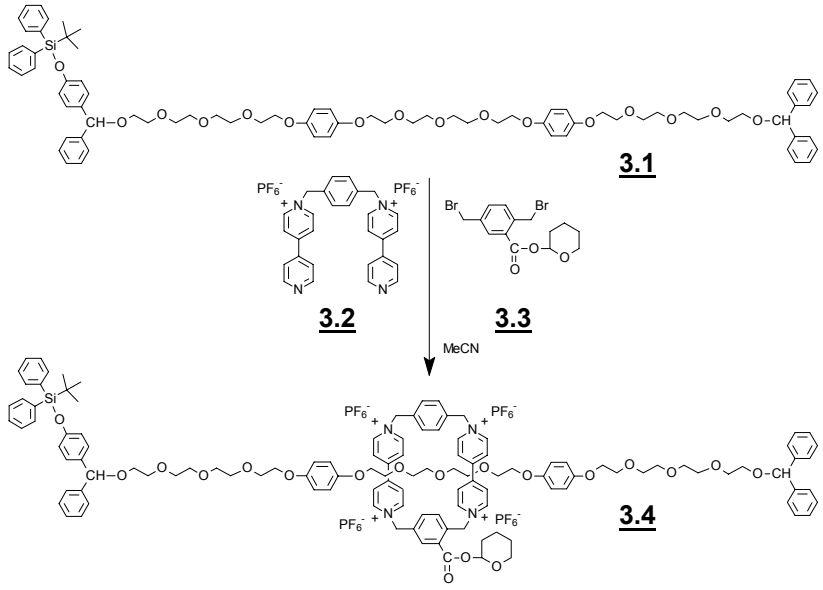
In the second part of this chapter, the synthesis and characterization of this new monomer and the dimer will be discussed. We have introduced a spacer group between the carboxylic acid and the cyclophane to reduce any steric or electronic effects and we have used the allyl ester instead of the THP ester because of its higher stability. The rotaxane dimer was obtained via the selective deprotection of the two functional groups in separate batches and subsequent coupling.

Finally, the stability of the redesigned rotaxane will be discussed. We have found that a slow degradation of the dumbbell part takes place. Recommendations for a more stable dumbbell are made.

[†] M. P. L. Werts, M. van den Boogaard, G. Hadziioannou and G. M. Tsivgoulis, *Chem. Comm*. **1999**, 623.

3.2 Rotaxane monomer with a TBDPS-protected phenol and a THP-protected carboxylic acid

In this paragraph, we will describe the synthesis of the rotaxane monomer bearing a TBDPS-protected phenol and a THP-protected carboxylic acid, following the design described in chapter 2. The reaction for the preparation of the rotaxane is based on the 'clipping' procedure, depicted in scheme 3.1.



Scheme 3.1. *Reaction scheme for the synthesis of the biprotected rotaxane monomer **3.4**.*

In particular, the electron deficient paraquat dication **3.2** forms a complex with the electron-rich hydroquinone groups in the dumbbell **3.1**. Subsequently, the paraquat dication reacts with the THP-protected 2,5-bis(bromomethyl)benzoic acid **3.3** to close the ring and form the rotaxane **3.4**. The synthesis of the dumbbell-shaped molecule **3.1**, tetrahydropyranyl-2,5-bis(bromomethyl)benzoate **3.3** and the rotaxane will be discussed in detail. The synthesis of the paraquat dication **3.2** has been described in literature.[1]

The synthesis of the asymmetric dumbbell **3.1** requires nine reaction steps in contrast to the 'symmetric' rotaxane where only four steps are necessary. Even though partial deprotection and silyl migration takes place during the synthesis, due to the very basic conditions used, we are able to prepare the dumbbell in reasonable yields.

In the second part of this paragraph, we will deal with the preparation of compound **3.3**. The first step in the synthesis is the bromination of 2,5-dimethylbenzoic acid. This

reaction gives many byproducts and so the product is only obtained in a low yield. It was possible to increase the yield by modifying the reaction conditions and improving the purification procedure.

After the preparation of all the starting materials, the synthesis of the rotaxane **3.4** is presented. We obtained this rotaxane in a 3 % yield and the 'symmetric' derivative in 20 % yield. The difference in yield can be attributed to steric effects in the functionalized cyclophane unit.

As we will see at the end, the THP-ester is not stable enough and deprotection occurs during the rotaxane synthesis. Furthermore, the carboxylic acid functionality, which is attached directly to the cyclophane, is not very reactive towards esterification due to electronic and steric effects.

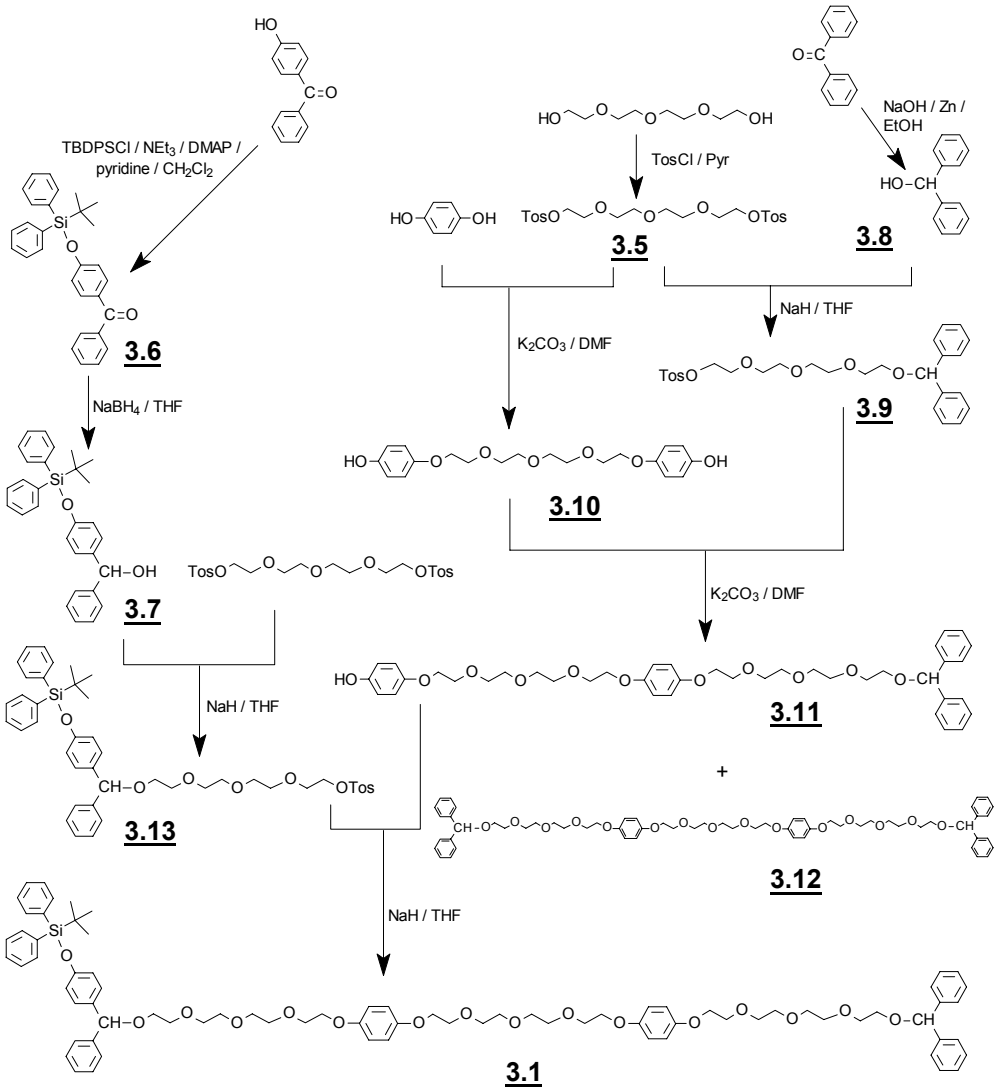
3.2.1 Synthesis of the dumbbell-shaped molecule

The dumbbell comprises an ethylene glycol chain with two hydroquinone units as the active parts for the 'clipping' procedure. At both ends, the chain is endcapped with two diphenylmethane blocking groups of which one bears the protected phenol functionality. Our approach to the synthesis of this compound is shown in scheme 3.2. The starting materials are the inexpensive chemicals benzophenon, 4-hydroxybenzophenon, tetraethylene glycol and hydroquinone.

After the protection of the phenol moiety in 4-hydroxybenzophenon with TBDPS,[2,3] the two blocking groups were prepared via the reduction of the ketone group and subsequent coupling with tetraethylene glycol. In parallel, the 'middle part' of the dumbbell, bearing two hydroquinone units, was prepared. The final coupling of this 'middle part' with the two blocking groups in two steps yields the dumbbell **3.1**.

Tetraethyleneglycol bis(4-methylbenzenesulfonate) **3.5**[4] (Tos–E4–Tos) and benzhydrol[5] **3.8** were synthesized according to literature procedures.

The reduction of the ketone **3.6** to the alcohol **3.7** must be mild since the silyl ether can be cleaved under very basic conditions. Sodium boronhydride ($NaBH_4$) is a mild reducing agent and gave the substituted benzhydrol **3.7** in a good yield (79 %).



Scheme 3.2. *Reaction scheme for the synthesis of the dumbbell-shaped molecule **3.1**.*

One advantage of the proposed synthetic route is that the synthesis of **3.9**, **3.10**, **3.11**, **3.13** and **3.1** are all based on the same general reaction, the etherification of a hydroxy group with a tosylate. The alcohol group, either aliphatic or aromatic, is reacted with a tosylate to form an ether bond. The two reactions of the blocking groups with Tos–E4–Tos to produce **3.9** and **3.13** involve the reaction of an *aliphatic* alcohol, so a strong base is needed, e.g. NaH. Unfortunately, it was observed that under these basic conditions, some deprotection of the

TBDPS ether takes place. By using a 100 % excess of Tos–E4–Tos, in order to minimize the synthesis of disubstituted derivatives, the product **3.13** was obtained in a reasonable yield. The product was purified by column chromatography and isolated in a 65 % yield.

For the preparation of the other three products (**3.10**, **3.11** and **3.1**) a phenoxide instead of an alkoxide is needed and thus less strong bases can be used. In order to find the best conditions, the coupling of Tos–E4–Tos with hydroquinone to obtain tetraethyleneglycol dihydroquinone **3.10** was explored under several reaction conditions. The use of potassium *tert*-butoxide (*t*-BuOK) or sodium hydride (NaH) as bases in THF gave low yields probably due to precipitation of the phenoxide. So the more polar solvent DMF was used in combination with potassium carbonate (K_2CO_3) to give **3.10** in a 55 % yield. If NaH is used instead of K_2CO_3, the yield decreases to 25 %.

Products **3.11** has also been synthesized using K_2CO_3 in DMF. The yield is moderate, mainly because a mixture of mono- and disubstituted compound is formed. The disubstituted side product **3.12** has a similar structure as the final product **3.1**, except for the absence of the functional group. This compound was used to synthesize a 'symmetric' rotaxane bearing no functional groups.

The last reaction step to synthesize the dumbbell shaped molecule **3.1**, was performed with NaH in THF instead of K_2CO_3 in DMF. The advantage of NaH is the higher reactivity, which reduces the reaction time, compared to K_2CO_3. This diminishes the possibility for silyl migration for which we found prove after fractionation of the reaction mixture by column chromatography. Beside the product **3.1**, several byproducts were obtained (figure 3.1). Intermolecular silyl migration from **3.1** or **3.13** to **3.11** takes place, yielding the deprotected form of compound **3.13**, the deprotected dumbbell **3.14** and the TBDPS protected compound **3.15**. Furthermore, **3.14** can react again with **3.13** to yield **3.16**, which is also found as a byproduct. The ^{1}H-NMR spectra of these compounds are shown in figure 3.1. Silyl groups are known to be able to migrate from one hydroxyl to another. Conditions that favor silyl migration are the presence of a strong base in protic solvents, but migration in aprotic solvents is also observed.[6,7,8] Although the silyl migration cannot be prevented completely, the reduction of the reaction time to 2 hours gives a mixture of product and starting materials, which can be separated by column chromatography, with a minimum amount of byproducts. The starting materials **3.11** and **3.13** can be recovered and reused.

As was discussed in the beginning of this paragraph, three chemical parts are needed for the synthesis of the rotaxane. The first part was the dumbbell-shaped molecule **3.1**. The next step involves the preparation of the two parts necessary for the synthesis of the functionalized cyclophane ring.

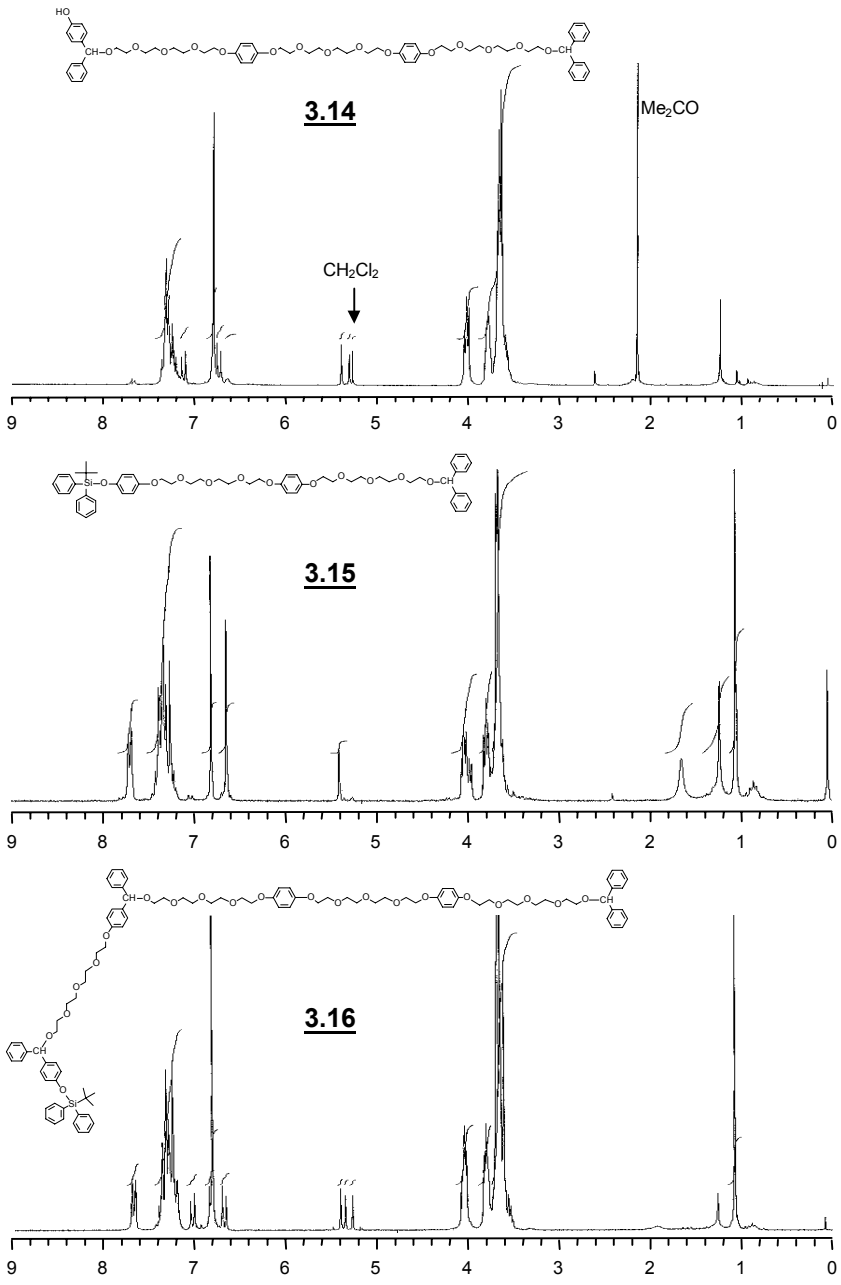


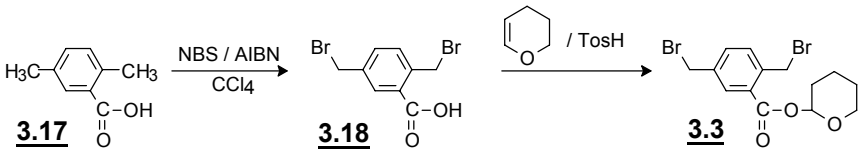
Figure 3.1. *^{1}H-NMR spectra of three side products found during the synthesis of **3.1**.*

3.2.2 Synthesis of the cyclophane derivatives

In order to synthesize the rotaxane via the 'clipping' procedure, two parts of the cyclophane ring must be prepared, which later on will react in the presence of the dumbbell-shaped molecule **3.1**. One part is the paraquat dication **3.2**, which was prepared according to a literature procedure.[1] The other part is a carboxyl-functionalized derivative of 1,4-bis(bromomethyl)benzene. The carboxylic acid group was protected with DHP. The reaction procedure that was followed for its synthesis is shown in scheme 3.3 and consists of two steps, 1) the bromination of 2,5-dimethylbenzoic acid and 2) the subsequent protection of the carboxylic acid group with DHP.

3.2.2.1 Bromination of 2,5-dimethylbenzoic acid

Although the synthesis of 2,5-bis(bromomethyl)benzoic acid **3.18** is described in literature,[9] we observed that it is very sensitive to the reaction conditions and that several byproducts are formed. Similar results have also been found by others.[10] The product is prepared via the bromination of 2,5-dimethylbenzoic acid with *N*-bromosuccinimide in CCl_4 in the presence of a radical initiator. We have repeated the described procedure using azobisisobutyronitrile (AIBN) as a radical initiator several times.



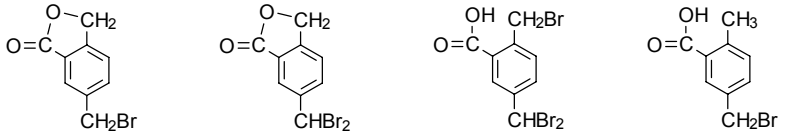
Scheme 3.3. *Reaction scheme for the preparation of the THP-protected 2,5-bis(bromomethyl)benzoic acid **3.3**.*

Analysis of the crude reaction mixture by ^{1}H-NMR shows six different products, namely the starting material **3.17**, the product **3.18**, 6-bromomethylphthalide **3.19**, 6-dibromomethylphthalide **3.20**, 5-dibromomethyl-2-bromomethylbenzoic acid **3.21** and 5-bromomethyl-2-methylbenzoic acid **3.22** (figure 3.2). After fractionation of the reaction mixture by column chromatography, three products can be isolated, which were characterized as the starting material **3.17**, 6-bromomethylphthalide **3.19** and 6-dibromomethylphthalide **3.20**. The phthalides are the result of the intramolecular esterification of the carboxylic acid and the adjacent bromomethylene. The formation of this stable cyclic ester (lactone), takes place spontaneously since both groups are in close vicinity within the molecule.[11] So the acid

3.18 is converted to the phthalide **3.19** and **3.21** is converted to **3.20**. The disappearance of the brominated dimethylbenzoic acids **3.18** and **3.21** after column chromatography suggests that they were converted to the phthalides on the silica column, thus another purification method was necessary.

After removal of the succinimide by filtration, the crude reaction mixture is dissolved in CH_2Cl_2/acetone and hexane is slowly added. Increase of the amount of hexane leads to the precipitation of 5-dibromomethyl-2-bromomethylbenzoic acid **3.21**, 6-dibromomethyl-phthalide **3.20**, the product 2,5-bis(bromomethyl)benzoic acid **3.18**, 6-bromomethylphthalide **3.19** and the starting material 2,5-dimethylbenzoic acid **3.17**, in this order. The 5-bromomethyl-2-methylbenzoic acid **3.22** is usually present only in small quantities.

In this way all products could be obtained and characterized separately. The chemical shifts in the ^{1}H-NMR spectra of the product and byproducts are listed in table 3.1. By successive precipitations, 90 % pure product **3.18** could be obtained with an isolated yield of 10 %.



3.19 **3.20** **3.21** **3.22**

Figure 3.2. *Byproducts formed in the synthesis of 2,5-bis(bromomethyl)benzoic acid **3.18**: 6-bromomethylphthalide **3.19**, 6-dibromomethylphthalide **3.20**, 5-dibromomethyl-2-bromomethylbenzoic acid **3.21** and 5-bromomethyl-2-methylbenzoic acid **3.22**.*

Table 3.1. *^{1}H-NMR chemical shifts (ppm) of the products formed in the synthesis of 2,5-bis(bromomethyl)benzoic acid **3.18**.*

Compound	Ar–C_2	Ar–C_5	Ar–H_3[a]	Ar–H_4[b]	Ar–H_6[c]
3.18	4.99 (CH_2)	4.50 (CH_2)	7.50 (d)	7.61 (dd)	8.16 (d)
3.19	5.33 (CH_2O)	4.56 (CH_2)	7.49 (d)	7.72 (dd)	7.93 (d)
3.20	5.63 (CH_2O)	7.71 (CH)	7.53 (d)	7.96 (dd)	8.09 (d)
3.21	4.99 (CH_2)	6.64 (CH)	7.55 (d)	7.70 (dd)	8.27 (d)
3.22	2.50 (CH_3)	4.57 (CH_2)	7.51 (d)	7.80 (dd)	7.92 (d)

[a] $^3J_{3,4}$ = 7.7 Hz, [b] $^3J_{4,3}$ = 7.9 Hz; $^4J_{4,6}$ = 2.6 Hz, [c] $^4J_{6,4}$ = 2.6 Hz.

To increase the yield, we have modified the reaction procedure so that smaller amounts of byproducts would be formed. The products **3.20** and **3.21** are both the result of three brominations, once on the C2 methyl and two times on the C5 methyl. Because these two byproducts are the most difficult to separate from the product, the amount of added NBS was lowered from 2.2[9,10,12,13] to 1.7 equivalents, which resulted in the decrease of tribrominated compounds. Adding the NBS in four portions over a period of 1.5 hours could further improve this result. Under these conditions the reaction mixture contained besides the product **3.18**, the starting material **3.17** and 5-bromomethyl-2-methylbenzoic acid **3.22** as the main byproducts. After purification, the pure product was obtained in a 25 % yield.

3.2.2.2 THP-protection of 2,5-bis(bromomethyl)benzoic acid

The next step in the synthesis of **3.3** involves the THP-protection of the carboxylic acid group. Several attempts using the same conditions as for model compounds (2 equivalents of dihydropyran in THF) gave only a very low yield of 5 %. Most probably, the carboxylate group becomes more acidic due to the strong electron-withdrawing character of the bromine groups. This enhances the cleavage of the THP-ester. An additional problem during this reaction is the slow conversion of the carboxylic acid into the lactone. Both these problems were solved by using dihydropyran as the solvent, which gives a 100 % yield in 10 minutes at 0 °C.

The product is not stable for long periods of storage, because it is slowly deprotected and converted to the lactone. The HBr liberated in the lactonization catalyses further deprotection. The product is stable in the presence of a base that scavenges the produced HBr. To prevent nucleophilic substitution of the bromine by the base, it should be sterically hindered. So the product can be stored without degradation in a hexane/diisopropylethylamine (DIPEA) solution.

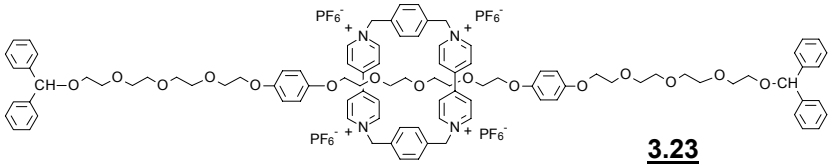
3.2.3 Preparation and characterization of the rotaxane

In the previous paragraphs, the synthesis of the separate parts of the rotaxane was described. Starting from these three compounds, the next step is the synthesis of the rotaxane monomer as depicted in scheme 3.1.

3.2.3.1 Synthesis of the rotaxane

The half-cyclophane **3.2** and the THP-protected 2,5-bis(bromomethyl)benzoic acid **3.3** were reacted in the presence of the dumbbell-shaped molecule **3.1** in MeCN (scheme 3.1). DIPEA was added to maintain basic conditions in order to prevent cleavage of the THP ester. In four days, the reaction mixture changed from light yellow to light red. The red color is characteristic for cyclophane-based rotaxanes and can be assigned to a charge transfer between the cyclophane and the hydroquinone in the dumbbell.[14] Successive precipitations with CH_2Cl_2 and Et_2O yielded the rotaxane monomer **3.4** as a red solid in a 3 % yield.

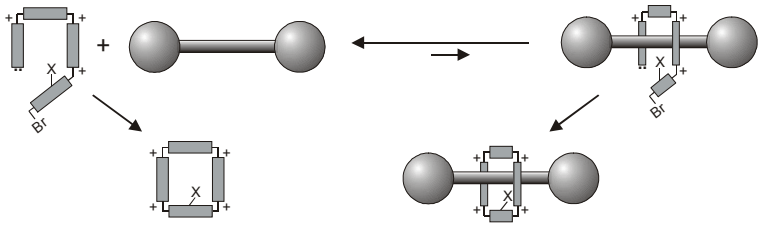
For comparison reasons, the 'symmetric' analog **3.23** was synthesized, starting from the unfunctionalized dumbbell **3.12**, the paraquat dication **3.2** and *p*-bis(bromomethyl)benzene. Under similar reaction conditions, a surprisingly high yield of 20 % was obtained, indicating that the presence of the functional groups has a large effect on the rotaxane formation.



3.23

Figure 3.3. *'Symmetric' rotaxane **3.23**.*

The difference in yields can be explained when we visualize the reaction as shown in scheme 3.4 (the THP ester is depicted as X). The first step (not shown) is the reaction of the paraquat dication with the functionalized bis(bromomethyl)benzene to form a trication.



Scheme 3.4. *Schematic representation of the synthesis of the rotaxane and the effect of steric hindrance.*

This can either be as a complex around the dumbbell or non-complexed in solution. The equilibrium between these two situations will depend on a) electronic effects and b) steric

effects. The importance of the steric effects will be maximized in the second coupling that will close the ring. Here the presence of the substituent X probably creates a significant steric hindrance. Ashton *et al*. found a similar result[9] as the yield of their pseudorotaxane decreased from 35 to 7 % when an ester group was incorporated into the cyclophane unit (figure 3.4). So closing of the ring will mainly occur in the uncomplexed trication, resulting in a low yield for the rotaxane.

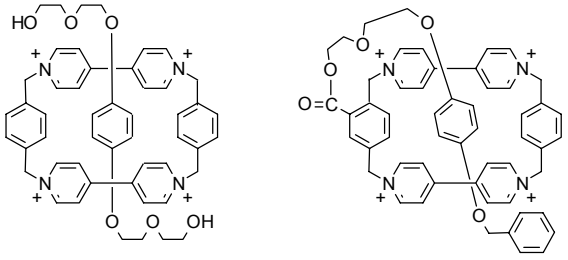


Figure 3.4. *Two pseudorotaxanes synthesized by Ashton et al.*[9]

3.2.3.2 Characterization of the rotaxane

The UV–Vis absorption spectrum of the rotaxane monomer in MeCN (figure 3.5) shows two absorption maxima. The strong absorption in the UV region at 265 nm is due to the aromatic groups in the rotaxane. At 466 nm, a weak absorption is observed, which can be attributed to the charge transfer between the π-systems of the hydroquinone donor in the dumbbell and the cyclophane acceptor, indicating that the rotaxane is formed.

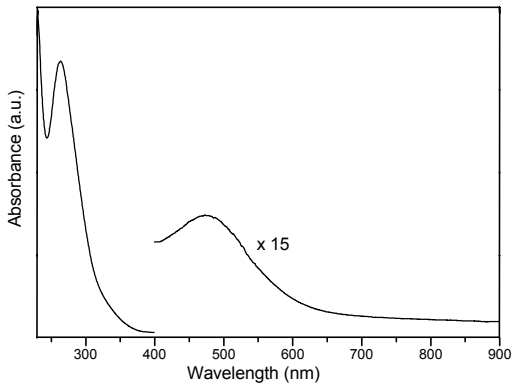


Figure 3.5. *UV–Vis absorption spectrum of the rotaxane monomer **3.4** in MeCN.*

In the ^{1}H-NMR spectrum of the rotaxane, peaks corresponding to the dumbbell as well as to the cyclophane unit can be assigned. The absence of the sharp singlet of the hydroquinone units in the dumbbell at 6.81 ppm is characteristic for this type of rotaxane. The shuttling of the cyclophane over the hydroquinone groups occurs at a frequency, similar to the timescale of the NMR measurement. As a result, this peak is merged into the baseline.[15,16] The silane protective group shows characteristic peaks at 1.20, 7.53 and 7.82 ppm. However, the large multiplet centered around 1.7 ppm corresponding to the THP protective group is not observed. To check if the THP group is indeed deprotected, Matrix Assisted Laser Desorption Ionisation Time-of-Flight (MALDI-TOF) mass spectrometry was employed.

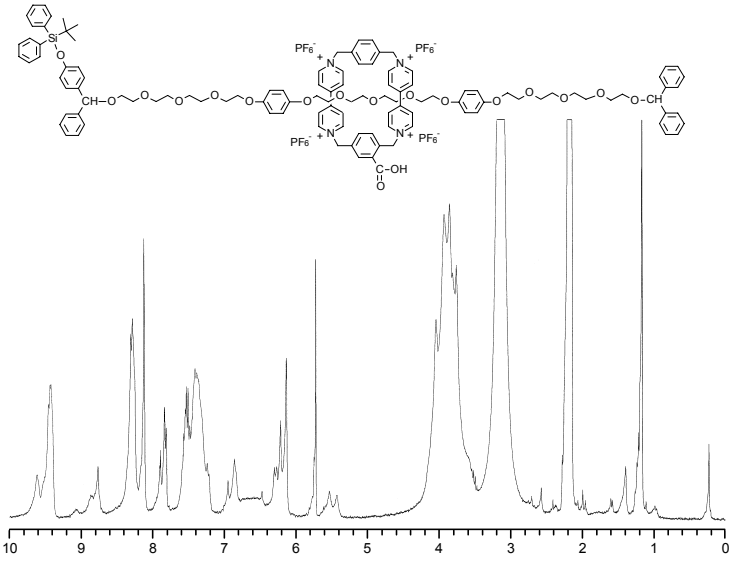


Figure 3.6. *^{1}H-NMR spectrum of the rotaxane monomer **3.4**. No peak can be observed at 1.7 ppm, indicating that the THP ester has been deprotected.*

Because cyclophane-based rotaxanes show distinct differences in MALDI-TOF spectra compared to most other molecules, we will first compare the spectra of a standard protein and the 'symmetric' rotaxane **3.23**. Bovine serum albumin (BSA) has a molecular weight of 66431 g.mol^{-1}. Except for the parent peak, peaks are observed at 33216 g.mol^{-1} and 22157 g.mol^{-1}, exactly half and one third of the mass, respectively. It corresponds to the protein with a charge of +2 and +3, as can be predicted from the theory of mass spectrometry.

The MALDI-TOF spectrum of the rotaxane shows three distinct peaks at 1584, 1729 and 1874 g.mol^{-1}, each separated by 145 g.mol^{-1}. The lowest mass corresponds to the rotaxane without any counterion, the second to the rotaxane with 1 PF_6^- and the third to the rotaxane

with 2 PF_6^-. The expected charges of these species are +4, +3 and +2 respectively, so the corresponding peaks should be **396** (= 1584 ÷ 4**)**, **576** (= 1729 ÷ 3) and **937** (= 1874 ÷ 2) $g.mol^{-1}$. These positions are indicated by arrows in figure 3.7b. The fact that these peaks are not observed, can only be explained by the assumption that all species have a charge +1, independent of the number of counterions. This is due to the low electrochemical potential of the viologen part of the cyclophane, which is reduced very easily.[17,18] Probably a large part of the molecules is reduced completely and has no charge. These molecules will not be detected in MALDI-TOF, while a small part still has a charge +1 and is observed in the spectra. As a result, a low signal-to-noise ratio is usually observed. The peaks at lower masses correspond to fragments of the rotaxane.

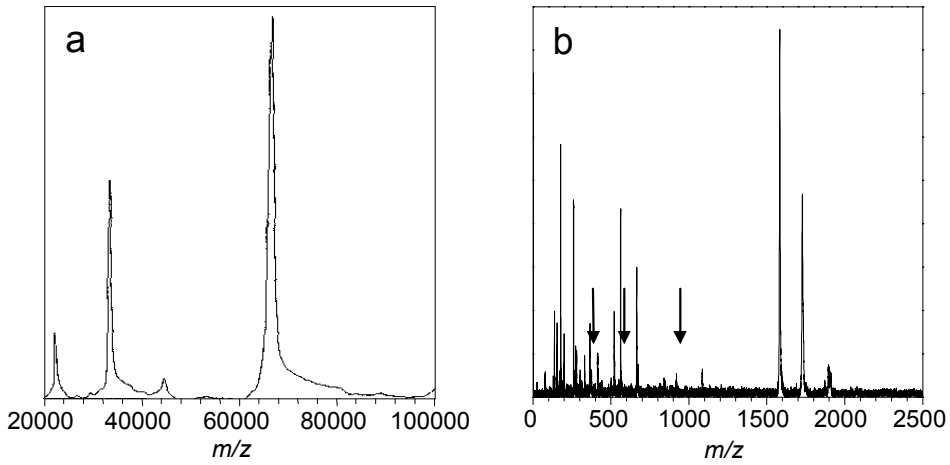


Figure 3.7. *Two examples of MALDI-TOF spectra for a) bovine serum albumin[19] and b) the 'symmetric' rotaxane **3.23**.*

Figure 3.8 shows the MALDI-TOF spectrum of the rotaxane monomer. Multiple peaks are observed at *m/z* 1882, 2027 and 2172 respectively, corresponding to the product without the THP protective group, which has lost four, three and two PF_6^- counterions.† Therefore, MALDI-TOF spectrometry shows that the carboxylic acid group is deprotected as it was found from the ^{1}H-NMR spectrum. The deprotection could have taken place either during the synthesis or workup, despite the fact that basic conditions were used. The increased

† Small peaks at 2592 and 2737 were found which correspond to the mass of a [3]rotaxane, bearing *two* cyclophane units. From these studies however, it cannot be concluded whether these peaks are indeed from the [3]rotaxane or from a cluster of the [2]rotaxane with a free cyclophane, formed during the MALDI-TOF experiment.

lability of the THP protective group must be found in the strong electron-withdrawing effect of the cyclophane. As for the THP-protected 2,5-bis(bromomethyl)benzoic acid, the electron-withdrawing substituents increase the acidity of the carboxylic acid and thus favor deprotection. This effect is even stronger in the cyclophane and deprotection can occur even under basic conditions. Therefore, we concluded that the THP group is too labile and cannot be used for the synthesis of a biprotected rotaxane monomer, even though it is stable in model reactions.

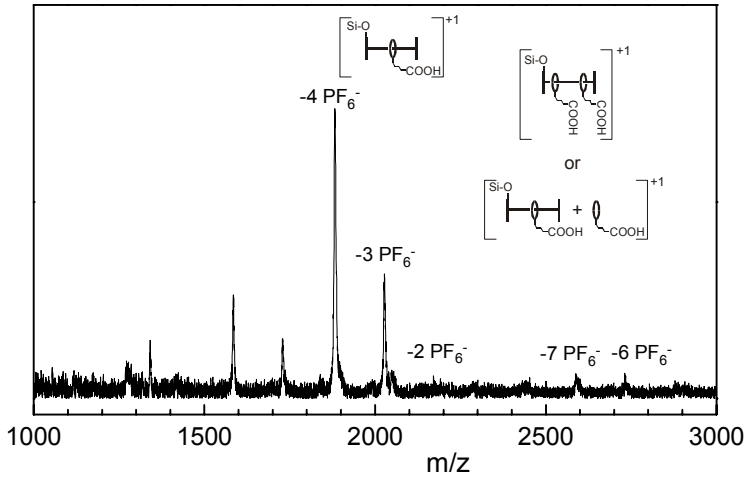


Figure 3.8. *MALDI-TOF spectrum of the rotaxane monomer **3.4**. The two major peaks at 1882 and 2027 correspond to the rotaxane in which the carboxylic acid is deprotected.*

3.2.3.3 Reactivity of the rotaxane – Esterification of the carboxylic acid group

Recent results from Menzer *et al.*[20] showed that the esterification of carboxylic acid-functionalized cyclophanes is very difficult. They have attempted to synthesize a polycatenane, starting from a catenane, bearing a carboxylic acid-functionalized cyclophane and a phenol-functionalized crownether (figure 3.9). Esterification of these two groups should give a polymer. However, a number of attempts under different reaction conditions never gave a oligocatenane. 'Unfavorable stereoelectronic effects, which decrease the reactivity of the functional groups attached to the [2]catenane monomers', were proposed as a possible explanation. Several similarities can be found between their difunctional catenane and our difunctional rotaxane. In both structures, the carboxylic acid is directly linked to the cyclophane and must react with a phenol. Therefore, some experiments on model compounds

were performed in order to study the feasibility of the esterification of the cyclophane carboxylic group.

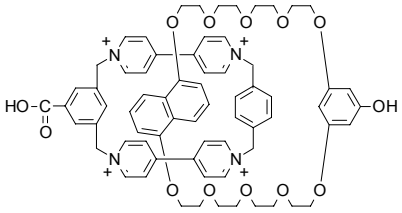
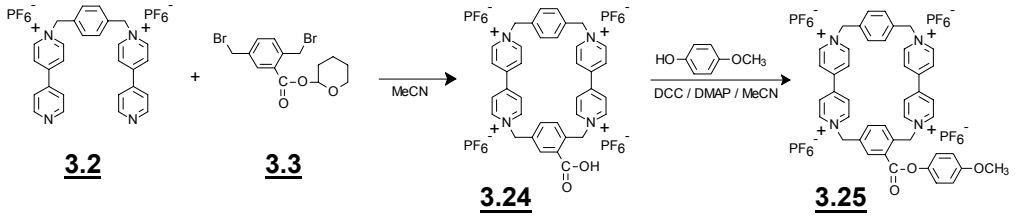


Figure 3.9. *A difunctional [2]catenane as synthesized by Menzer et al.*[20] *Polycondensation should yield a polycatenane but has never been achieved.*

We have synthesized the carboxylic acid-functionalized cyclophane starting from the paraquat dication **3.2** and the THP-protected 2,5-bis(bromomethyl)benzoic acid **3.3**. Again the acid is deprotected during the reaction as ^{1}H-NMR indicated. Esterification with *p*-methoxyphenol was attempted with dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP).[21,22] After 3 days, only 45 % of the cyclophane was found to be converted to the ester, according to ^{1}H-NMR. The low yield for the esterification can be attributed to either a) the increased acidity of the carboxylate group by the strong electron-withdrawing pyridinium groups or b) steric effects. The same effects were also responsible for the deprotection of the THP group in the cyclophane and the difficult protection of 2,5-bis(bromomethyl)benzoic acid with DHP.



3.2 **3.3** **3.24** **3.25**

Scheme 3.5. *Reaction scheme for the synthesis of the carboxylic acid-functionalized cyclophane and its p-methoxyphenol ester.*

In this paragraph we have described the synthesis of the dumbbell-shaped molecule **3.1**, the THP-protected 2,5-bis(bromomethyl)benzoic acid **3.3** and the rotaxane **3.4**. Although the synthesis of these materials is not easy, we have managed to obtain both **3.1** and **3.3** in reasonable quantities. The rotaxane synthesis proceeded in a poor 3 % yield, which we have attributed to steric hindrance of the cyclophane substituents. Furthermore, it was found that the

THP protective group for the carboxylic acid is deprotected during the synthesis, most probably due to the strong electron-withdrawing character of the pyridinium groups in the cyclophane. This electronic effect in combination with steric reasons makes it difficult to esterify this group to synthesize rotaxane oligomers. So, the functionality on the cyclophane needs to be redesigned in order to increase its reactivity.

3.3 Rotaxane monomer and dimer with a TBDPS-protected phenol and an allyl-protected carboxylic acid

To increase the reactivity of the carboxylic acid, it was decided to add a spacer group between the electron-withdrawing substituents and the acid functionality, hereby diminishing electronic problems. Furthermore, this modification is expected to reduce the steric hindrance, which might decrease the reactivity of the carboxylic acid. Because the THP ester is too labile, it was decided to replace it by the allyl ester. Model reactions indicated that this group can also be used as protective group for the carboxylic acid (§ 2.4.2.3).

First, the selection of an appropriate spacer group will be discussed. Two different spacer lengths (hydroxyacetate and hydroxybutanoate) have been tested and the latter was found suitable to our purpose. Simultaneously, the protective group was changed from THP to allyl, which is more stable.

The final part of this section concerns the synthesis of the new rotaxane monomer and its sequential deprotection and coupling to obtain a rotaxane dimer.

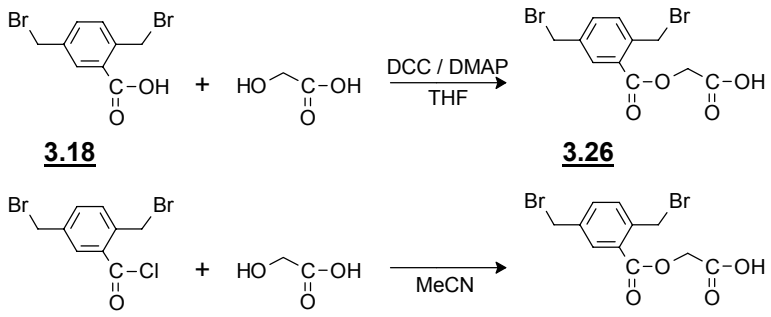
3.3.1 Rotaxane monomer with TBDPS and allyl protective group

3.3.1.1 Selection of the spacer group

The purpose of the spacer is to diminish steric and electronic effects of the cyclophane on the carboxylic acid and so to increase the reactivity of the functional group. The spacer is incorporated by reacting an appropriate molecule with 2,5-bis(bromomethyl)-benzoic acid. This molecule needs to bear i) a functional group, capable to react with the acid group in 2,5-bis(bromomethyl)benzoic acid and ii) a new carboxylic acid group.

Initially, hydroxyacetic acid was chosen as the spacer group between the cyclophane and the carboxylic acid. This compound can be esterified with 2,5-bis(bromomethyl)benzoic acid to yield the product **3.26**, which can subsequently be protected (scheme 3.6).

The esterification reaction between hydroxyacetic acid and **3.18** has been attempted, using two different methods, i) the direct esterification between the acid and alcohol with DCC and DMAP and ii) the coupling of 2,5-bis(bromomethyl)benzoyl chloride with hydroxyacetic acid. Preliminary experiments showed that both reactions did not yield the desired product and that the phthalide **3.19** (figure 3.2) was produced instead. No additional studies were made on this reaction but the introduction of another spacer group, 4-hydroxybutanoate, was investigated.



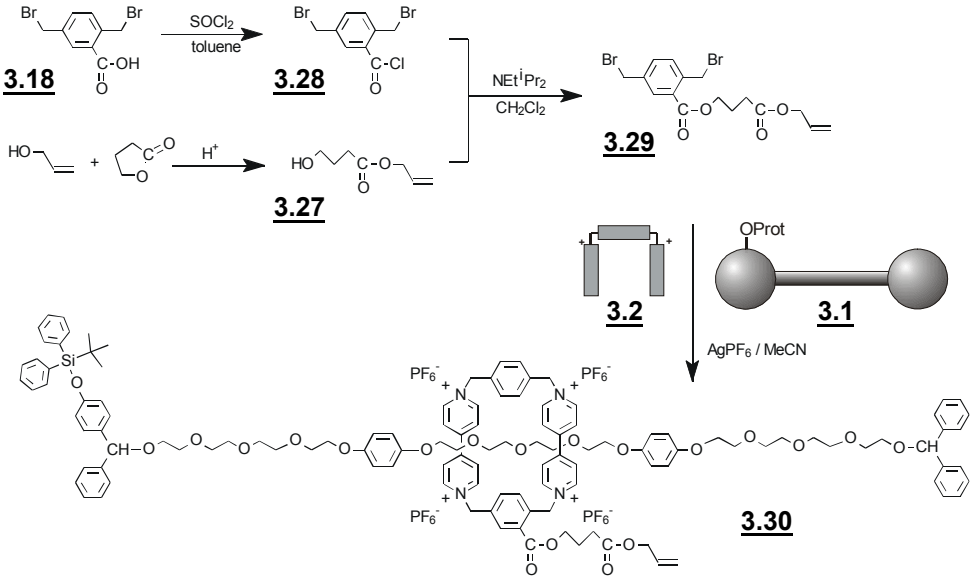
Scheme 3.6. *Attempted reaction to introduce the hydroxyacetate spacer between the carboxylic acid group and the cyclophane.*

One way to introduce the hydroxybutanoate spacer is to start from γ-butyrolactone (scheme 3.7). We decided to first protect the acid group in this molecule and in a next step to couple it with 2,5-bis(bromomethyl)benzoic acid. Thus, γ-butyrolactone was reacted with an excess of allylalcohol to form allyl-4-hydroxybutanoate **3.27** in a 30 % yield. On the other hand, 2,5-bis(bromomethyl)benzoic acid was converted to the acid chloride **3.28** using thionylchloride and subsequently reacted with **3.27** to yield allyl-4-butanoate-2,5-di(bromomethyl)benzoate **3.29** in a 49 % yield. Since this product is stable, it can easily be purified by column chromatography. For this reason, crude 2,5-bis(bromomethyl)benzoic acid **3.18** can be used and purified as the compound **3.29** in the latter step. So for the synthesis of **3.29**, a mixture containing ~60 % of 2,5-bis(bromomethyl)benzoic acid was used, which also explains the low yield of this reaction.

3.3.1.2 Synthesis of the new rotaxane monomer

The rotaxane **3.30** was synthesized in a similar manner as the previous rotaxane **3.4**. Initially, a trication is formed, which bears 2 PF_6^- and 1 Br^- counterions. To prevent

precipitation of this intermediate in MeCN, $AgPF_6$ was added to the reaction mixture.[†] After a reaction time of 4 days, the precipitated AgBr was removed by centrifugation, followed by the addition of chloroform to the supernatant to precipitate the paraquat dication and the uncomplexed cyclophane. The rotaxane was separated from the unreacted dumbbell by precipitation with Et_2O. Column chromatography of the rotaxane with MeOH: 2M NH_4Cl: $MeNO_2$ and subsequent ion exchange with NH_4PF_6 gave the rotaxane **3.30** in a 5 % yield. The rotaxane is a red solid, soluble in acetone, acetonitrile, dichloromethane, DMF, DMSO and chloroform and insoluble in water, methanol, ethanol and diethylether. When the rotaxane is converted to the chlorine salt, it is soluble in methanol, ethanol, water and DMF.



Scheme 3.7. *Reaction scheme for the synthesis of the rotaxane **3.30**.*

The rotaxane monomer was further characterized by ^{1}H-NMR spectroscopy and MALDI-TOF mass spectrometry. ^{1}H-NMR spectroscopy (figure 3.10) shows again peaks corresponding to both the dumbbell (e.g. ethylene glycol at 3.60–4.15 ppm) and the cyclophane unit (e.g. *p*-phenylene at 8.16 ppm and α-H pyridinium at 9.43–9.49 and 9.59 ppm) in a 1:1 ratio. Both protective groups can be identified by their characteristic peaks; 7.56

[†] Model reactions with TBDPS-protected methoxyphenol show that 98 % pure $AgPF_6$ causes partial deprotection of the silane group. Since silanes are easily deprotected with fluoride-ions, most likely AgF is present in the $AgPF_6$ as an impurity. This problem can be solved by using 99.99 % pure $AgPF_6$, which indeed doesn't give any deprotection.

and 7.85 ppm for the TBDPS protective group and 4.70–4.76, 5.34–5.55 and 6.10 ppm for the allyl protective group. The peaks corresponding to the hydroquinone units in the dumbbell are merged in the baseline. A complete assignment of the spectrum is given in the experimental section.

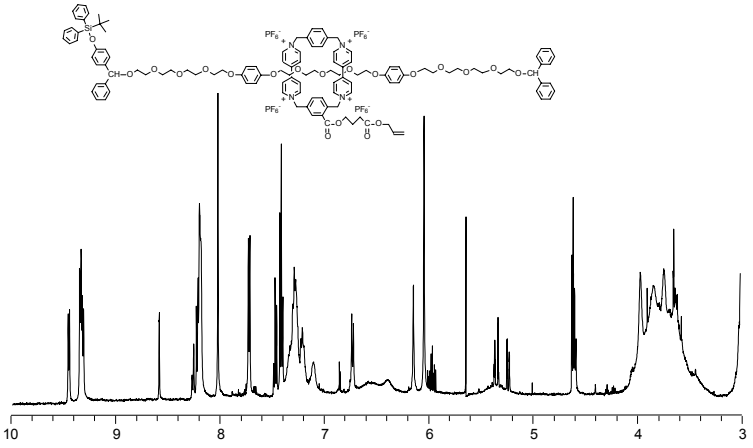


Figure 3.10. *Partial ^{1}H-NMR spectrum of the rotaxane monomer **3.30**.*

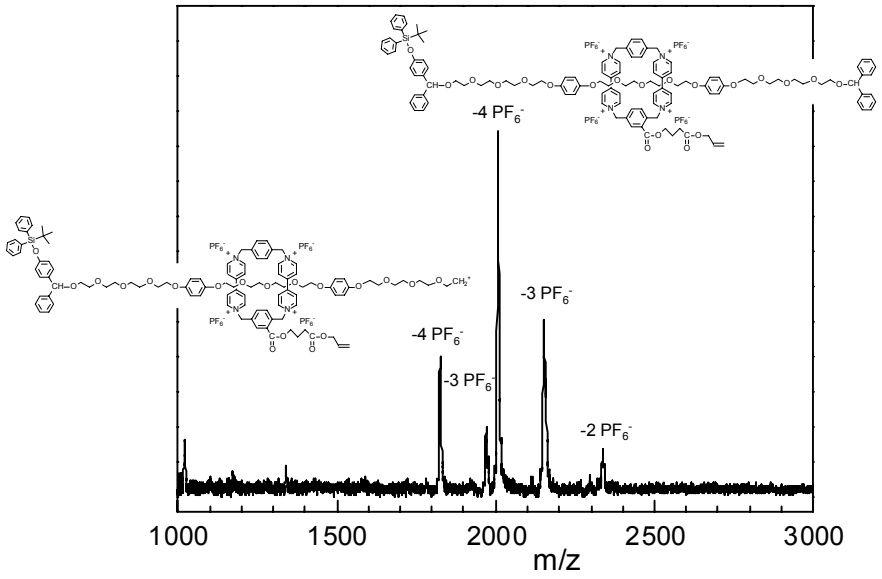
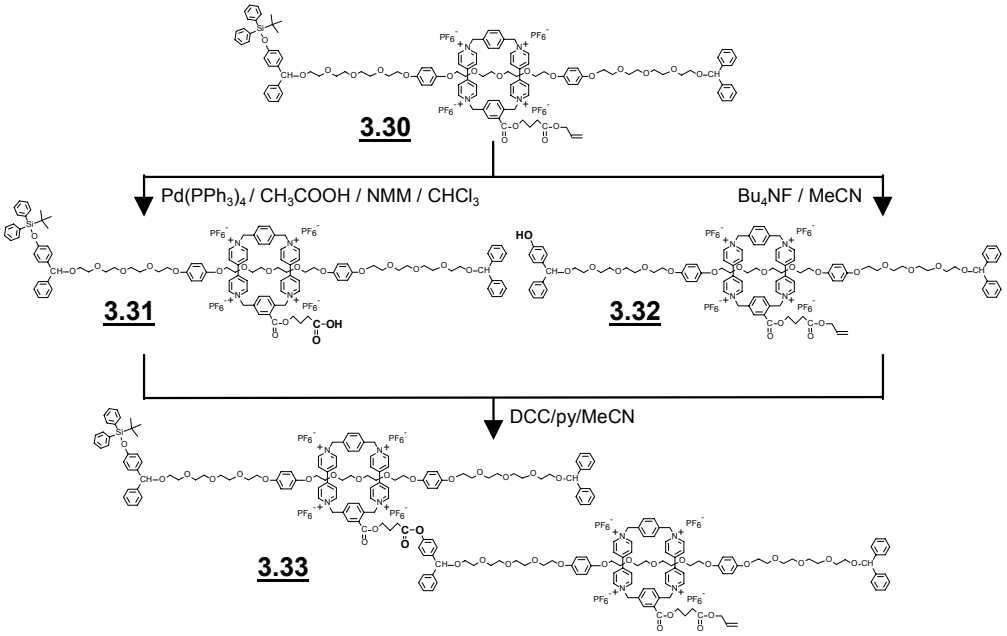


Figure 3.11. *MALDI-TOF spectrum of the rotaxane **3.30**. Fragmentation takes place at the C–O bond next to the diphenylmethane blocking group.*

The MALDI-TOF spectrum (figure 3.11) shows peaks at 2009 $[M - 4\ PF_6]^+$, 2153 $[M - 3\ PF_6]^+$ and 2298 $[M - 2\ PF_6]^+$, corresponding to the rotaxane monomer bearing both protective groups. The peaks at lower masses (1825, 1970 and 2125) are the result of fragmentation of the product during the measurement.

3.3.2 Synthesis of a rotaxane dimer

The successful preparation of the rotaxane monomer, containing two stable protective groups, which can be removed selectively, permitted us to synthesize rotaxane oligomers. For the deprotection and esterification reactions, the same methods as for the model compounds were used. Particularly, in one batch, the phenol was deprotected by the cleavage of the silyl ether using tetrabutylammonium fluoride (scheme 3.8). One equivalent of *o*-nitrophenol was added to protonate the deprotected phenol since the produced phenoxide can react with the cyclophane unit. In a second batch, the carboxylic acid group was deprotected using tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$). The deprotection rate was found to be lower than in the model reactions. We have used 60 and 30 equivalents of acetic acid and *N*-methylmorpholine, respectively, instead of 4 and 2 to have complete deprotection in 3 hours.



Scheme 3.8. *Reaction scheme for the preparation of the two deprotected monomers and the synthesis of the dimer.*

Both deprotected rotaxanes **3.31** and **3.32** were obtained in a 80 % yield after extraction with CH_2Cl_2/H_2O and precipitation from $CHCl_3/Et_2O$. The dimer **3.33** was synthesized by reacting the two deprotected monomers in MeCN with pyridine and DCC. Although DMAP is a much better catalyst for esterifications,[21,22] we have avoided its use, since it might be reactive towards cyclophanes.[23]

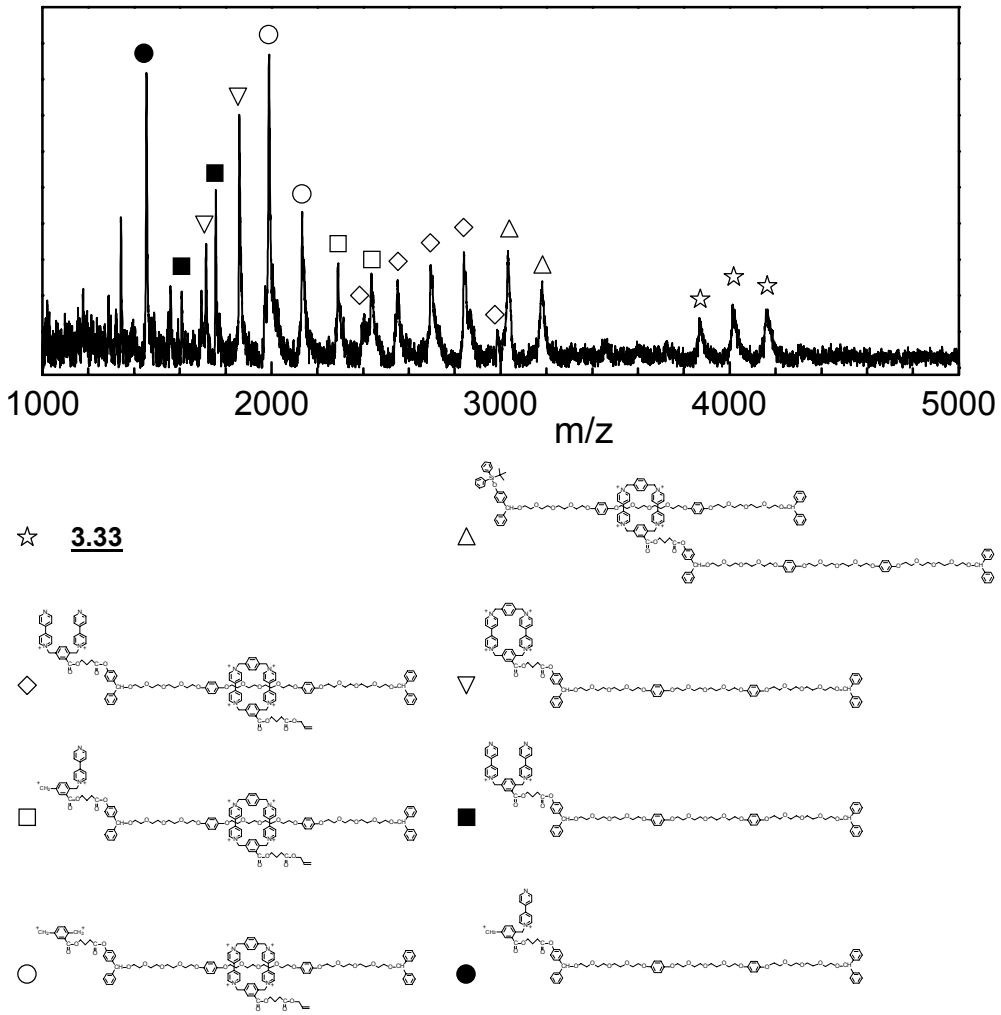


Figure 3.12. *MALDI-TOF spectrum of the rotaxane dimer **3.33**. Besides the peaks corresponding to the product, peaks are observed which can be identified as fragments of the dimer.*

After purification by column chromatography, the dimer was obtained in a 30 % yield, which is low compared to model reactions, done under the same conditions. The reason for the low yield is a side reaction in which the *O*-acylurea intermediate, formed in the reaction between the carboxylic acid and DCC, is converted to the inactive *N*-acylurea. This will be discussed in detail in chapter 4.

The rotaxane dimer was identified by MALDI-TOF mass spectrometry, which shows peaks at *m/z* 3866 $[M - 7\ PF_6]^+$, 4011 $[M - 6\ PF_6]^+$ and 4156 $[M - 5\ PF_6]^+$, corresponding to the product. In figure 3.12, several tens of peaks at lower masses are also observed. These are related to fragments of the dimer, mostly formed by degradation of the cyclophane ring in the MALDI-TOF mass spectrometer.

^{1}H-NMR spectroscopy shows a similar spectrum as for the monomer, but integration of the peaks indicates that there is one TBDPS protective group and one allyl protective group for two rotaxane units. Furthermore, the peak of the CH_2-group adjacent to the carboxylate group in the spacer shows now two signals, since there is one CH_2-group connected to an aliphatic ester (the allyl group) and one to an aromatic ester (the dimer linkage).

3.3.3 Stability of the rotaxane

As was stated already in § 2.3.1, we have chosen the cyclophane–polyether thread based rotaxane, which is prepared via the 'clipping' procedure. One advantage of this method is the fact that the dumbbell, which needs many reaction steps to be synthesized, can be recovered. However, in the synthesis of rotaxane **3.30**, only 20–50 % of the dumbbell was recovered, most probably due to degradation. Surprisingly, control experiments showed that the dumbbell was stable under the reaction conditions used for the synthesis of the rotaxane (4 days in MeCN/$AgPF_6$). Since this degradation takes place during the synthesis, it cannot easily be prevented. Therefore, we have determined which part of the dumbbell is the weakest in order to redesign and synthesize a more stable dumbbell.

From two different observations it was concluded that the weakest part in the dumbbell is the diphenylmethane ether bond. First, we found that diphenylmethoxy-tetraethylene glycoltosylate **3.9** is not stable at room temperature for a prolonged time. Although no investigation of the actual side reaction of this product was made, a mixture of several products was observed in thin layer chromatography. Second, the MALDI-TOF spectrum of the rotaxane **3.30** shows besides the expected peaks at 2009, 2153 and 2298, corresponding to $[M - 4\ PF_6]^+$, $[M - 3\ PF_6]^+$ and $[M - 2\ PF_6]^+$ also peaks at lower masses (figure 3.11). These peaks at 1825, 1970 and 2125 correspond to the rotaxane, which has lost the unsubstituted blocking group. Apparently, the substituted blocking group is more stable since the electron-withdrawing silyl ether stabilizes the ether bond.

Although the fragmentation in MALDI-TOF follows completely different mechanisms than the degradation of compound **3.9**, both show that the diphenylmethane ether bond is the weakest part in the dumbbell. Thus, an alternative, more stable blocking group has to be used. The synthesis and characterization of rotaxanes based on this new dumbbell are presented in the next chapter.

3.4 Conclusions and outlook

Initially, we have synthesized the rotaxane monomer that was proposed in chapter 2, based on a cyclophane–polyether thread rotaxane with diphenylmethane blocking groups. The preparation of the separate parts of the rotaxane, namely the dumbbell and the THP-protected bis(bromomethyl)benzoic acid were described. The synthesis of the dumbbell is mainly based on the etherification of an alkoxide and a tosylate. Precautions should be taken to minimize deprotection and silyl migration of the phenol protective group, which occurs under the basic conditions used in the etherification. Despite the silyl migration, we have synthesized the dumbbell in reasonable yields.

The next step was the synthesis of the molecule **3.3**, which will react with the paraquat dication to form the cyclophane. This product was synthesized by the bromination of 2,5-dimethylbenzoic acid and subsequent protection of the acid group with THP. We have studied the former reaction extensively. Besides the dibrominated product, also the mono- and tribrominated products as well as phthalides are formed. Furthermore, 2,5-bis(bromomethyl)-benzoic acid was found to be converted to the lactone during column chromatography. By modification of the reaction procedure and repetitive precipitations, a 90 % pure product can be obtained in a 25 % yield.

Reaction of the dumbbell, the paraquat dication and the THP-protected 2,5-bis(bromomethyl)benzoic acid yielded the rotaxane, bearing a TBDPS-protected phenol in the dumbbell and a carboxylic acid in the cyclophane unit, in a 3 % yield. The low yield is a consequence of the substitution on the cyclophane, which increases steric hindrance. In addition, deprotection of the carboxylic acid occurred during the synthesis of the rotaxane. This can be attributed to the increased acidity of the carboxylate. The carboxylic acid is also found not to be reactive towards esterification, due to similar reasons.

To increase the reactivity of the carboxylic acid, we have extended the distance between the carboxylic acid group and the cyclophane by the introduction of a spacer. Moreover, we have used a more stable protective group, i.e. the allyl group. The allylbutanoate-functionalized 2,5-bis(bromomethyl)benzoic acid is stable and can easily be purified in a moderate yield, this in contrary to the THP-protected compound, which gives

deprotection and lactone formation in solution and during column chromatography. The new rotaxane **3.30** was synthesized in a 5 % yield.

By selective deprotection of the two functional groups, we have obtained two monofunctionalized rotaxanes, which could be esterified to form the rotaxane dimer, as was identified both by ^{1}H-NMR spectroscopy and MALDI-TOF mass spectrometry.

The intention of this research was to synthesize well-defined oligomers and to study their mechanical behavior. However, no oligomers longer than the dimer were made. Although the yield for the rotaxane is low, which makes production on large scale not feasible, the dumbbell can in principle be recovered and reused in a new reaction. This is important because the dumbbell is very time-consuming and difficult to synthesize. As described in § 3.3.3, only 20–50 % of the dumbbell can be recovered each time after the purification of the rotaxane, which is most probably caused by cleavage of the diphenylmethane ether bond. It appeared that the blocking group we have used did not allow us to prepare oligomers with a larger number of repeating units than two, the dimer. Thus, we decided to search other possible blocking groups. This is described in chapter 4.

3.5 Experimental

Measurements

For general remarks see Chapter 2. UV–Vis spectra were recorded on a SLM Aminco 3000. MALDI-TOF spectra were taken on a Micromass TofSpec E mass spectrometer using dihydroxybenzoic acid (DHB) as matrix. Elemental analyses were carried out at the Microanalytical Department of the University of Groningen. High resolution mass spectra (HRMS) were obtained from a JEOL MS Route JMS-600H.

Materials and methods

Tetraethyleneglycol bis(4-methylbenzenesulfonate)[4] **3.5,** benzhydrol[5] **3.8** and the paraquat dication **3.2**[1] were obtained according to literature procedures. DMF was distilled three times over P_2O_5.

4-(*tert*-butyl-diphenylsiloxy)benzophenon 3.6

Pyridine (8.4 ml, 100 mmol) was added to a solution of *tert*-butylchlorodiphenylsilane (7.2 ml, 28 mmol) in dry THF (15 ml) and stirred for 15 min. This solution was added dropwise to a solution of 4-hydroxybenzophenon (5.0 g, 25 mmol), triethylamine (3.8 ml, 28 mmol) and DMAP (0.15 g, 1.25 mmol) in dry THF (35 ml) at 0 °C over a period of 0.5 hour. After 5 hours at room temperature, the solution was concentrated, Et_2O was added and extracted with 0.1 N HCl and H_2O. The organic layer was dried over $MgSO_4$, the solvent removed in vacuum

and recrystallized from hexane, yielding the product as white crystals (10.0 g, 92 %). ^{1}H-NMR: δ 1.11 (s, 9H), 6.81 (d, 2H), 7.33–7.54 (m, 9H), 7.63 (d, 2H), 7.67–7.74 (m, 6H); anal. calcd for $C_{29}H_{28}O_2Si$: C 79.78, H 6.47, found: C 79.89, H 6.57.

[4-(*tert*-butyl-diphenylsiloxy)phenyl]phenylmethanol 3.7

3.6 (3.20 g, 7.33 mmol) was dissolved in dry THF (25 ml). $NaBH_4$ (83 mg, 2.20 mmol) was added and the reaction mixture was refluxed for 7 hours. After cooling down, Et_2O was added, washed with H_2O and dried over $MgSO_4$. Evaporation of the solvent in vacuum and column chromatography [SiO_2, hexane:Et_2O (3:1)] yielded the product as a clear oil (2.54 g, 79 %). ^{1}H-NMR: δ 1.13 (s, 9H), 2.19 (d, 1H), 5.74 (d, 1H), 6.76 (d, 2H), 7.11 (d, 2H), 7.24–7.50 (m, 11H), 7.74 (d, 4H); HRMS $C_{29}H_{30}O_2Si$ calcd 438.2026, found 438.2015.

2-(2-(2-(2-(diphenylmethoxy)ethoxy)ethoxy)ethoxy)ethoxytosylate 3.9

A solution of **3.8** (1.47 g, 8 mmol) in THF (10 ml) was added to a suspension of NaH (0.35 g, 8.8 mmol) in THF (5 ml) and refluxed for 2 hours after which it was added dropwise to a refluxing solution of **3.5** (6.03 g, 12 mmol) over a period of 0.5 hour. After 2 hours, the reaction mixture was concentrated, CH_2Cl_2 was added and extracted with H_2O. The organic phase was dried over $MgSO_4$ and the solvent evaporated in vacuum. After column chromatography [SiO_2, Et_2O] the product was isolated as a gray oil (1.60 g, 39 %). ^{1}H-NMR: δ 2.43 (s, 3H), 3.54–3.72 (m, 14H), 4.13 (t, 2H), 5.40 (s, 1H), 7.21–7.37 (m, 12H), 7.78 (d, 2H); HRMS $C_{28}H_{34}O_7S$ calcd 514.2025, found 514.2018.

dihydroquinone tetraethyleneglycol 3.10

Hydroquinone (11.0 g, 100 mmol) and **3.5** (5.03 g, 10 mmol) were dissolved in dry DMF (50 ml). After the addition of K_2CO_3 (2.90 g, 21 mmol) the reaction mixture was stirred for 15 hour at 80 °C. The solvent was removed in vacuum and the resultant brown oil was dissolved in CH_2Cl_2 and extracted with H_2O. The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuum. The resulting oil was dissolved in warm chloroform, and after cooling down, the excess hydroquinone was filtered off. The filtrate was subjected to column chromatography [SiO_2, Et_2O:CH_2Cl_2 (2:1)], yielding a clear oil (2.1 g, 55 %). ^{1}H-NMR: δ 3.67 (s, 8H), 3.75 (t, 4H), 3.92 (t, 4H), 6.67 (d, 8H).

1-{*p*-[2-(2-(2-(2-(diphenylmethoxy)ethoxy)ethoxy)ethoxy)ethoxy]phenoxy}-13-{*p*-hydroxyphenoxy}-3,6,9-trioxaundecane 3.11

A solution of **3.9** (0.80 g, 1.5 mmol), **3.10** (1.14 g, 3 mmol) and K_2CO_3 (0.41 g, 3 mmol) in dry DMF (20 ml) was stirred for 20 hours at 80 °C. The solvent was removed in vacuum and the resulting brown oil was dissolved in CH_2Cl_2 and washed with H_2O. The organic layer was dried over Na_2SO_4 and the solvent removed in vacuum. Column chromatography [SiO_2,

CH_2Cl_2:acetone 9:1] yielded the product as a gray oil (0.48 g, 45 %). ^{1}H-NMR: δ 3.60–3.84 (m, 26H), 3.95–4.08 (m, 6H), 5.40 (s, 1H), 6.71 (s, 4H), 6.78 (d, 4H), 7.21–7.37 (m, 10H). The disubstituted product **3.12** could be isolated in a 20 % yield. ^{1}H-NMR: δ 3.59–3.73 (m, 32H), 3.78–3.84(m, 8H), 4.02–4.18 (m, 8H), 5.40 (s, 2H), 6.81 (s, 8H), 7.22–7.38 (m, 20H).

2-(2-(2-(2-([4-(*tert*-butyl-diphenylsiloxy)phenyl]phenylmethoxy)ethoxy)ethoxy)ethoxy) ethoxytosylate 3.13

A suspension of NaH (0.25 g, 6.3 mmol) in dry THF (10 ml) was added to a solution of **3.7** (2.50 g, 5.7 mmol) in dry THF (15 ml). After stirring for 10 min, this solution was added to a refluxing solution of **3.5** (5.73 g, 11.4 mmol) in dry THF (40 ml) and refluxing was continued for 3 hours. The reaction mixture was concentrated in vacuum, extracted with CH_2Cl_2/H_2O and dried over $MgSO_4$. Concentration of the organic layer and column chromatography [SiO_2, $CHCl_3$:Et_2O (11:1)] yielded the product as a light-yellow oil (2.85 g, 65 %). ^{1}H-NMR: δ 1.13 (s, 9H), 2.41 (s, 3H), 3.54–3.65 (m, 14H), 4.12 (t, 2H), 5.27 (s, 1H), 6.68 (d, 2H), 7.10 (d, 2H), 7.22–7.40 (m, 13H), 7.68 (d, 4H), 7.77 (d, 2H).

[1-{*p*-[2-(2-(2-(2-(diphenylmethoxy)ethoxy)ethoxy)ethoxy)ethoxy]phenoxy}-13-{*p*-[2-(2-(2-(2-([4-(*tert*-butyl-diphenylsiloxy)phenyl]phenylmethoxy)ethoxy)ethoxy)ethoxy)ethoxy] phenoxy}-3,6,9-trioxaundecane 3.1

A suspension of NaH (75 mg, 1.87 mmol) in dry THF (8 ml) was added to a solution of **3.11** (1.23 g, 1.7 mmol) in dry THF (20 ml). After stirring for 10 min, this solution was added to a refluxing solution of **3.13** (1.31 g, 1.7 mmol) in dry THF (25 ml) and refluxing was continued for 2 hours. The reaction mixture was concentrated, extracted with CH_2Cl_2/H_2O and dried over $MgSO_4$. Concentration of the organic layer and column chromatography [SiO_2, CH_2Cl_2:acetone (9:1)] yielded the product as a light-yellow oil (0.80 g, 36 %). ^{1}H-NMR: δ 1.08 (s, 9H), 3.52–3.73 (m, 32H), 3.78–3.83 (m, 8H), 4.00–4.07 (m, 8H), 5.27 (s, 1H), 5.40 (s, 1H), 6.67 (d, 2H), 6.81 (s, 8H), 7.03 (d, 2H), 7.19–7.40 (m, 13H), 7.67 (d, 4H).

2,5-bis(bromomethyl)benzoic acid 3.18

2,5-dimethylbenzoic acid (5.00 g, 33.3 mmol), *N*-bromosuccinimide (2.52 g, 14.2 mmol) and benzoylperoxide (171 mg, 0.71 mmol) were dissolved in CCl_4 (100 ml) and refluxed. A red color appeared which disappeared again after 15 minutes. NBS (2.52 g) and BPO (171 mg) were added and refluxing was continued. NBS (2.52 g) and BPO (171 mg) were added two more times after 15 and 45 minutes. Each time a red color appeared which disappeared again after some time. The reaction mixture was refluxed for 30 minutes after the last addition and then cooled down fast. The solid was filtered off and the filtrate concentrated in vacuum. The solid was dissolved in CH_2Cl_2:acetone (3:1) and precipitated with hexane (30 ml). The precipitate was filtered off, dissolved in CH_2Cl_2:acetone (3:1) and again precipitated with

hexane (40 ml). The product was filtered off as an off-white solid (2.6 g, 25 %). ^{1}H-NMR: δ 4.50 (s, 2H), 4.99 (s, 2H), 7.50 (d, 1H), 7.61 (dd, 1H), 8.16 (d, 1 H).

(3,4-dihydro-2H-pyranyl)-2,5-bis(bromomethyl)benzoate 3.3

Dihydropyran (1 ml) was cooled to 0 °C. **3.18** (500 mg, 1.62 mmol) and *p*-toluenesulphonic acid (3 mg, 0.02 mmol) were added and the reaction mixture was stirred at room temperature for 10 minutes. Diisopropylethylamine (0.2 ml) was added to the reaction mixture, followed by hexane. The precipitate was filtered off and the filtrate was extracted with H_2O (until neutral pH). The organic phase was dried over Na_2SO_4 and the solvent was evaporated in vacuum, yielding a brown oil (635 mg, 100 %): ^{1}H-NMR: δ 1.52–1.97 (m, 6H), 3.23–3.86 (m, 1H), 3.95–4.11 (m, 1H), 4.50 (s, 2H), 4.96 (q, 2H), 6.26–6.33 (m, 1H), 7.45 (d, 1H), 7.55 (dd, 1H), 8.01 (d, 1H).

{[1-{*p*-[2-(2-(2-(2-(diphenylmethoxy)ethoxy)ethoxy)ethoxy)ethoxy]phenoxy}-13-{*p*-[2-(2-(2-(2-([4-(*tert*-butyl-diphenylsiloxy)phenyl]phenylmethoxy)ethoxy)ethoxy)ethoxy) ethoxy]phenoxy}-3,6,9-trioxaundecane][cyclo(2,5-(paraquat-*p*-phenylene-paraquat)benzoic acid)]rotaxane} tetrakis(hexafluorophosphate) 3.4

The dumbbell **3.1** (140 mg, 0.11 mmol) and **3.2** (75 mg, 0.11 mmol) were dissolved in dry MeCN (1.2 ml). **3.3** (60 mg, 0.11 mmol) and 2 drops NEt^iPr_2 were added, dissolved in dry MeCN (0.3 ml). After 4 days, the reaction mixture was centrifuged and the supernatant concentrated. CH_2Cl_2 was added and the precipitate removed by filtration. The solution was concentrated to 1 ml and the rotaxane precipitated with Et_2O (3 ml). The solid was redissolved in CH_2Cl_2 and precipitated with Et_2O two more times. After ion exchange with NH_4PF_6, the product was isolated as a red solid (11 mg, 3 %). ^{1}H-NMR (CD_3CN): δ 1.20 (s, 9H), 3.50–4.05 (m, 48H), 5.52 (s, 1H), 5.75 (s, 1H), 6.14 (s, 4H), 6.22 (s, 2H), 6.56 (s, 2H), 6.88 (d, 2H), 7.25–7.48 (m, 18H), 7.53 (m, 6H), 7.82 (d, 2H), 7.90 (s, 1H), 8.11 (s, 4H), 8.35 (s, 4H), 8.74 (s, 1H), 9.40–9.56 (m, 8H); No peaks corresponding to the THP protective groups were found; MALDI-TOF: 1882 $[M - 4\ PF_6]^+$, 2027 $[M - 3\ PF_6]^+$, 2172 $[M - 2\ PF_6]^+$ (corresponds to acid deprotected product).

cyclo(2,5-(paraquat-*p*-phenylene-paraquat)benzoic acid) tetrakis(hexafluorophosphate) 3.24

3.2 (88 mg, 0.125 mmol) and **3.3** (49 mg, 0.125 mmol) were dissolved in dry MeCN (1.2 ml) and 2 drops NEt^iPr_2 were added. After 3 days, the solid formed was washed with MeCN and dissolved in MeOH. $AgPF_6$ (79 mg, 0.31 mmol) was added and the solution stirred for 1 hour after which the solid was removed by centrifugation. Precipitation from MeCN/H_2O yielded the product (35 mg, 24 %). ^{1}H-NMR (CD_3CN): δ 5.72 (s, 4H), 5.90 (s, 2H), 6.12 (s, 2H), 7.54 (s, 4H), 7.62 (d, 1H), 7.80 (d, 1H), 8.17 (s, 1H), 8.32–8.45 (m, 8H), 8.84–9.02 (m, 8H).

cyclo(2,5-(paraquat-*p*-phenylene-paraquat)(*p*-methoxyphenol)benzoate) tetrakis (hexafluorophosphate) 3.25

To a solution of **3.24** (35 mg, 0.03 mmol) in dry MeCN (0.5 ml), *p*-methoxyphenol (3.8 mg, 0.03 mmol) and DMAP (0.2 mg, 0.002 mmol) were added. DCC (9.6 mg, 0.045 mmol) was added and the reaction mixture stirred for 3 days. The solid (DHU) was filtered off and CH_2Cl_2 (2 ml) was added to the solution. The product precipitated as a yellow solid (35 mg, 95 %). ^{1}H-NMR (CD_3CN): δ 3.77 (s, 3H)[a], 5.72 (s, 4H), 5.90 (s, 2H), 6.12 (s, 2H), 7.05 (dd, 4H) 7.54 (s, 4H), 7.62 (d, 1H), 7.75 (d, 1H), 8.25 (s, 1H), 8.32–8.45 (m, 8H), 8.84–9.02 (m, 8H).

[a] According to the integration of the peaks, only 45 % was converted to the ester.

allyl-4-hydroxybutanoate 3.27

Concentrated sulfuric acid (0.10 g, 1 mmol) was added to a mixture of butyrolactone (0.43 g, 5 mmol) and allylalcohol (2.9 g, 50 mmol) and stirred for 1 day. $NaHCO_3$ (0.1 g, 1 mmol) was added and the reaction mixture was stirred for another hour. Et_2O was added and extracted twice with 1M $NaHCO_3$ solution and H_2O, dried over $MgSO_4$ and the solvent evaporated in vacuum. Kugelrohr distillation (73 °C, 0.04 mm Hg) yielded the product as a clear liquid (0.21 g, 29 %). ^{1}H-NMR: δ 1.80 (quintet, 2H), 2.38 (t, 2H), 2.57 (s, 1H), 3.56 (t, 2H), 4.47 (d, 2H), 5.12 (d, 1H), 5.21 (d, 1H), 5.72–5.88 (m, 1H).

allyl-4-butanoate-2,5-bis(bromomethyl)benzoate 3.29

3.18 (0.21 g, 0.68 mmol) was suspended in dry toluene (10 ml). $SOCl_2$ (0.10 ml, 1.43 mmol) was added and refluxed for 1 hour. The reaction mixture was concentrated in vacuum, dissolved in dry CH_2Cl_2 (7 ml) and NEt^iPr_2 (0.13 ml, 0.82 mmol) and **3.27** (0.10 g, 0.68 mmol) were added. The reaction mixture was stirred overnight at room temperature, extracted with H_2O and dried over $MgSO_4$. Concentration of the organic layer and column chromatography [SiO_2, hexane:$CHCl_3$:Et_2O (8:3:1)] yielded the product as a light-yellow oil (0.15 g, 49 %). ^{1}H-NMR: δ 2.08 (m, 2H), 2.46 (m, 2H), 4.34 (m, 2H), 4.47 (dd, 2H), 4.53 (d, 2H), 4.90 (dd, 2H), 5.16 (d, 1H), 5.24 (d, 1H), 5.77–5.90 (m, 1H), 7.36–7.49 (m, 2H), 7.88 (d, 1H).

{[1-{*p*-[2-(2-(2-(2-(diphenylmethoxy)ethoxy)ethoxy)ethoxy)ethoxy]phenoxy}-13-{*p*-[2-(2-(2-(2-([4-(*tert*-butyl-diphenylsiloxy)phenyl]phenylmethoxy)ethoxy)ethoxy)ethoxy) ethoxy]phenoxy}-3,6,9-trioxaundecane][cyclo(2,5-(paraquat-*p*-phenylene-paraquat)(allyl-4-butanoate)benzoate)]rotaxane} tetrakis(hexafluoro-phosphate) 3.30

The dumbbell **3.1** (158 mg, 0.12 mmol) and **3.29** (52 mg, 0.12 mmol) were dissolved in dry MeCN (0.3 ml). $AgPF_6$ (70 mg, 0.28 mmol) and **3.2** (85 mg, 0.12 mmol), dissolved in dry MeCN (0.3 ml), were added. After 4 days, the reaction mixture was centrifuged and the

solution concentrated to 0.5 ml. By addition of $CHCl_3$ (4 ml), the paraquat dication and cyclophane precipitated. The solution was concentrated to 3 ml and Et_2O (1 ml) was added. The red precipitate was subjected to column chromatography [SiO_2, MeOH:2M NH_4Cl:$MeNO_2$ (7:2:1)] and after ion-exchange with NH_4PF_6, the product was obtained as a red solid (10 mg, 5 %). ^{1}H-NMR (CD_3CN): δ 1.20 (s, 9H), 2.38 (quintet, 2H), 2.77 (t, 2H), 3.60–4.15 (m, 48H), 4.70–4.76 (m, 4H), 5.22 (d, 1H), 5.28–5.43 (m, 3H), 6.10 (m, 1H), 6.27 (s, 4H), 6.48 (s, 2H), 6.52 (s, 2H), 6.88 (d, 2H), 7.23 (d, 2H), 7.34–7.61 (m, 21H), 7.85 (d, 4H), 8.16 (s, 4H), 8.30–8.40 (m, 10H), 8.71 (s, 1H), 9.43–9.49 (m, 6H), 9.59 (d, 2H); MALDI-TOF: 2009 $[M - 4\ PF_6]^+$, 2153 $[M - 3\ PF_6]^+$, 2298 $[M - 2\ PF_6]^+$; UV–Vis (MeCN): λ_{max} [nm] ($\varepsilon[M^{-1}cm^{-1}]$) = 265 (36000); 466 (650).

{[1-{*p*-[2-(2-(2-(2-(diphenylmethoxy)ethoxy)ethoxy)ethoxy)ethoxy]phenoxy}-13-{*p*-[2-(2-(2-(2-([4-(*tert*-butyl-diphenylsiloxy)phenyl]phenylmethoxy)ethoxy)ethoxy)ethoxy) ethoxy]phenoxy}-3,6,9-trioxaundecane][cyclo(2,5-(paraquat-*p*-phenylene-paraquat)-4-carboxybutylbenzoate)]rotaxane} tetrakis(hexafluorophosphate) 3.31

To a solution of **3.30** (10 mg, 3.9 µmol) in $CHCl_3$ (0.4 ml), acetic acid (13 µl, 230 µmol) and NMM (13 µl, 115 µmol) were added. A solution of $Pd(PPh_3)_4$ (9 mg, 7.7 µmol) in $CHCl_3$ (0.1 ml) was added and the reaction mixture was stirred for 3 hours, protected from light. After addition of $CHCl_3$ (3 ml) the rotaxane was precipitated with Et_2O (1 ml). The solid was extracted with CH_2Cl_2/H_2O and the solvent evaporated in vacuum, yielding the product as a red solid (7.8 mg, 80 %). ^{1}H-NMR (CD_3CN): δ 1.20 (s, 9H), 2.38 (quintet, 2H), 2.77 (t, 2H), 3.60–4.15 (m, 48H), 4.71 (t, 2H), 5.43 (s, 1H), 5.54 (s, 1H), 6.27 (s, 4H), 6.48 (s, 2H), 6.52 (s, 2H), 6.88 (d, 2H), 7.23 (d, 2H), 7.34–7.61 (m, 21H), 7.85 (d, 4H), 8.16 (s, 4H), 8.30–8.40 (m, 10H), 8.71 (s, 1H), 9.43–9.49 (m, 6H), 9.59 (d, 2H).

{[1-{*p*-[2-(2-(2-(2-(diphenylmethoxy)ethoxy)ethoxy)ethoxy)ethoxy]phenoxy}-13-{*p*-[2-(2-(2-(2-([4-hydroxyphenyl]phenylmethoxy)ethoxy)ethoxy)ethoxy)ethoxy]phenoxy}-3,6,9-trioxaundecane] [cyclo(2,5-(paraquat-*p*-phenylene-paraquat) (allyl-4-butanoate) benzoate)]rotaxane} tetrakis(hexafluorophosphate) 3.32

o-Nitrophenol (0.6 mg, 4.3 µmol) and Bu_4NF (9.5 µl, 9.5 µmol) were added to a solution of **3.30** (10 mg, 3.9 µmol) in MeCN (0.2 ml). After 30 minutes, the rotaxane was precipitated with H_2O and centrifuged. The solid was dissolved in $CHCl_3$ (2 ml) and precipitated with Et_2O (1 ml) twice, yielding the product as a red solid (6.4 mg, 70 %). ^{1}H-NMR (CD_3CN): δ 2.38 (quintet, 2H), 2.77 (t, 2H), 3.60–4.15 (m, 48H), 4.70–4.76 (m, 4H), 5.22 (d, 1H), 5.28–5.43 (m, 3H), 6.10 (m, 1H), 6.27 (s, 4H), 6.48 (s, 2H), 6.52 (s, 2H), 6.90 (d, 2H), 7.25 (d, 2H), 7.34–7.49 (m, 15H), 8.16 (s, 4H), 8.30–8.40 (m, 9H), 8.61 (s, 1H), 8.71 (s, 1H), 9.43–9.49 (m, 6H), 9.59 (d, 2H).

Dimer 3.33

3.31 (7.8 mg, 3.1 μmol) and **3.32** (6.4 mg, 2.7 μmol) were dissolved in MeCN (0.2 ml) and DCC (11 mg, 53 μmol) and pyridine (0.4 μl, 5 μmol) were added. After 7 days, DHU was removed by centrifugation and the product precipitated with $CHCl_3/Et_2O$. Column chromatography [SiO_2, MeOH:2M NH_4Cl:$MeNO_2$ (7:2:1)] and ion-exchange with NH_4PF_6 yielded the product as a red solid (4.4 mg, 32 %). ^{1}H-NMR (CD_3CN): δ 1.20 (s, 9H), 2.38 (m, 4H), 2.77 (m, 4H), 3.60–4.15 (m, 96H), 4.70–4.74 (m, 4H), 4.76–4.78 (m, 2H), 5.37 (d, 1H), 5.32–5.58 (m, 5H), 6.10 (m, 1H), 6.27 (s, 8H), 6.48 (s, 4H), 6.52 (s, 4H), 6.88 (d, 4H), 7.23–7.61 (m, 40H), 7.85 (d, 4H), 8.16 (s, 8H), 8.30–8.40 (m, 20H), 8.71 (s, 2H), 9.43–9.49 (m, 12H), 9.59 (d, 4H); MALDI-TOF: 3866 $[M - 7\ PF_6]^+$, 4011$[M - 6\ PF_6]^+$, 4156 $[M - 5\ PF_6]^+$; UV–Vis (MeCN): λ_{max} [nm] (ε[$M^{-1}cm^{-1}$]) = 265 (32000); 460 (550).

3.6 References

1. W. Geuder, S. Hünig and A. Suchy, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 489; *Tetrahedron* **1986**, *42*, 1665.
2. S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.* **1979**, 99.
3. Y. Guindon, C. Yoakim, M. A. Bernstein and H. E. Morton, *Tetrahedron Lett.* **1985**, *26*, 1185.
4. J. Dale and P. O. Kristiansen, *Acta Chem. Scand.* **1972**, *26*, 1471.
5. A. I. Vogel, *Practical Organic Chemistry*, third edition, Longmans, Green and co. ltd., London, **1956**.
6. K. K. Ogilvie and D. W. Entwistle, *Carbohydr. Res.* **1981**, *89*, 203.
7. S. S. Jones and C. B. Reese, *J. Chem. Soc., Perkins Trans 1*, **1979**, 2762.
8. W. Köhler and W. Pfleiderer, *Liebigs Ann. Chem.* **1979**, 1855.
9. P. R. Ashton, R. Ballardini, V. Balzani, S. E. Boyd, A. Credi, M. T. Gandolfi, M. Gómez-López, S. Iqbal, D. Philp, J. A. Preece, L. Prodi, H. G. Ricketts, J. F. Stoddart, M. S. Tolley, M. Venturi, A. J. P. White and D. J. Williams, *Chem. Eur. J.* **1997**, *3*, 152.
10. F. Vögtle, J. Grütze, R. Nätscher, W. Wieder, E. Weber and R. Grün, *Chem. Ber.* **1975,** *108,* 1694.
11. R. T. Morrison and R. N. Boyd, *Organic Chemistry*, Allyn and Bacon, Inc., Boston 1987, 874.
12. M. Newcomb, S. S. Moore and D. J. Cram, *J. Am. Chem. Soc.* **1977**, *99*, 6405.
13. A. C. Benniston and A. Harriman, *Synlett* **1993**, 223.
14. B. Odell, M. V. Redington, A. M. Z. Slawin, N. Spencer, J. F. Stoddart and D. J. Williams, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1547.

15. P.-L. Anelli, M. Asakawa, P. R. Ashton, R. A. Bissell, G. Clavier, R. Górski, A. E. Kaifer, S. J. Langford, G. Mattersteig, S. Menzer, D. Philp, A. M. Z. Slawin, N. Spencer, J. F. Stoddart, M. S. Tolley and D. J. Williams, *Chem. Eur. J.* **1997**, *3*, 1113.
16. P.-L. Anelli, N. Spencer and J. F. Stoddart, *J. Am. Chem. Soc.* **1991**, *113*, 5131.
17. D. H. Williams, A. F. Findesi, S. Naylor and B. W. Gibson, *J. Am. Chem. Soc.* **1987**, *109*, 1980.
18. T. M. Ryan, R. J. Day and R. G. Cooks, *Anal. Chem.* **1980**, *52*, 2054.
19. Tofspec E & SE Operator Manual, Micromass, 1996.
20. S. Menzer, A. J. P. White, D. J. Williams, M. Bělohradský, C. Hamers, F. M. Raymo, A. N. Shipway and J. F. Stoddart, *Macromolecules* **1998**, *31*, 295.
21. A. Hassner and V. Alexanian, *Tetrahedron Lett.* **1978**, *46*, 4475.
22. B. Neises and W. Steglich, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522.
23. A. R. Katritzky, *Tetrahedron* **1980**, *36*, 679.